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Clavicular Hypoplasia, Zygomatic Arch Hypoplasia, and Micrognathia: A Newly Defined Syndrome

Geralyn M. Ponzio,[1] and Michael L. Cunningham[2]*

[1]*University of Vermont College of Medicine, Burlington, Vermont*
[2]*Children's Craniofacial Center, Children's Hospital and Regional Medical Center and University of Washington Department of Pediatrics, Seattle, Washington*

We report on a 6-year-old boy with a previously undefined syndrome of clavicular hypoplasia, frontonasal malformation, zygomatic arch hypoplasia, micrognathia, and normal intelligence. His condition differs from similar syndromes on the basis of unique facial findings such as microcornea, stellate irises, and a midline maxillary cleft. We present his case, a review of the literature, and propose the acronym CHZAM, for clavicular hypoplasia, zygomatic arch, and micrognathia, to represent this syndrome. Am. J. Med. Genet. 92:200–205, 2000.

KEY WORDS: claviclar hypoplasia; zygomatic arch cleft; mandibulofacial dysostosis; micrognathia; microcornea; stellate iris; midline maxillary cleft; CCHA; CHZAM

INTRODUCTION

Prior to the identification of the CBFα1 mutation on chromosome 6 [Mundlos et al., 1996; Mundlos et al., 1997], Brueton et al. [1992] presented 3 patients with congenital clavicular hypoplasia or agenesis (CCHA) thought to have cleidocranial dysplasia due to chromosome 8q22 rearrangements [Brueton et al., 1992] and manifesting micrognathia, exopthalmos, and the lack of a generalized skeletal dysplasia. Because 8q22 was disrupted in all 3 patients, it was thought that the gene or genes responsible for the cleidocranial dysplasia phenotype might be located in this region. However, Mundlos et al. demonstrated no linkage to the 8q22 locus in 2 families with classical cleidocranial dysplasia and postulated that perhaps the CCHA phenotype present in these 3 patients, and in other CCHA-associated disorders, might be explained by multiple CCHA loci [Mundlos et al., 1995].

We present a patient with CCHA, frontonasal malformation, and micrognathia, findings common to cleidocranial dysplasia and individuals with 8q22 cytogenetic rearrangements. This patient also has findings common to those of Treacher Collins, Nager, and Miller Syndromes, mandibulofacial dysostosis (MFD) syndromes that include hypoplastic zygomatic arches, high-arched palate, and micrognathia. However, he lacks key diagnostic findings of any previously described CCHA or MFD syndrome, and does not have a CBFα1 mutation or cytogenetic rearrangement involving 8q22. We suggest that this patient's physical findings represent a new syndrome among disorders that involve CCHA and/or mandibulofacial dysostosis.

CLINICAL REPORT

C.G. was referred at birth for evaluation of facial abnormalities. He was the term 3.57-kg infant of a G3P2, 36-year-old woman. Prenatal exposures included occasional ethanol use, totaling approximately 10 drinks throughout pregnancy, and fewer than 10 cigarettes per day. Pregnancy was complicated by polyhydramnios; however, the fetal survey was normal by serial ultrasonography. Parents deny consanguinity. The patient has 2 sisters and 3 half-brothers, all of which are alive and well. Paternal history is unknown as the father was adopted; maternal family history is unremarkable.

The child was a healthy boy with weight, height, and head circumference all at the 50th centile. He had hypertelorism (interpupillary distance 5.0 cm, intercanthal distance of 3.5 cm, and an outer canthal distance of 8.5 cm, all >97th centile for age). Ophthalmologic findings included stellate irides, microcornea, and mild ptosis. The patient had a broad, bulbous nose, with a normal philtrum. There was a 5-mm midline alveolar diastema with a broad frenulum of the upper lip, an intact palate, and micrognathia, with hypoplastic condyles and incomplete temporomandibular joint formation. Though slightly posteriorly rotated, the ears were of normal size and shape (Fig. 1). His chest was well formed and symmetric without deformity. Cardiopul-

*Correspondence to: Dr. Michael L. Cunningham, Director, Children's Craniofacial Center, Division of Genetics and Development, CHRMC, CH-47, 4800 Sandpoint Way NE, Seattle, WA 98105.

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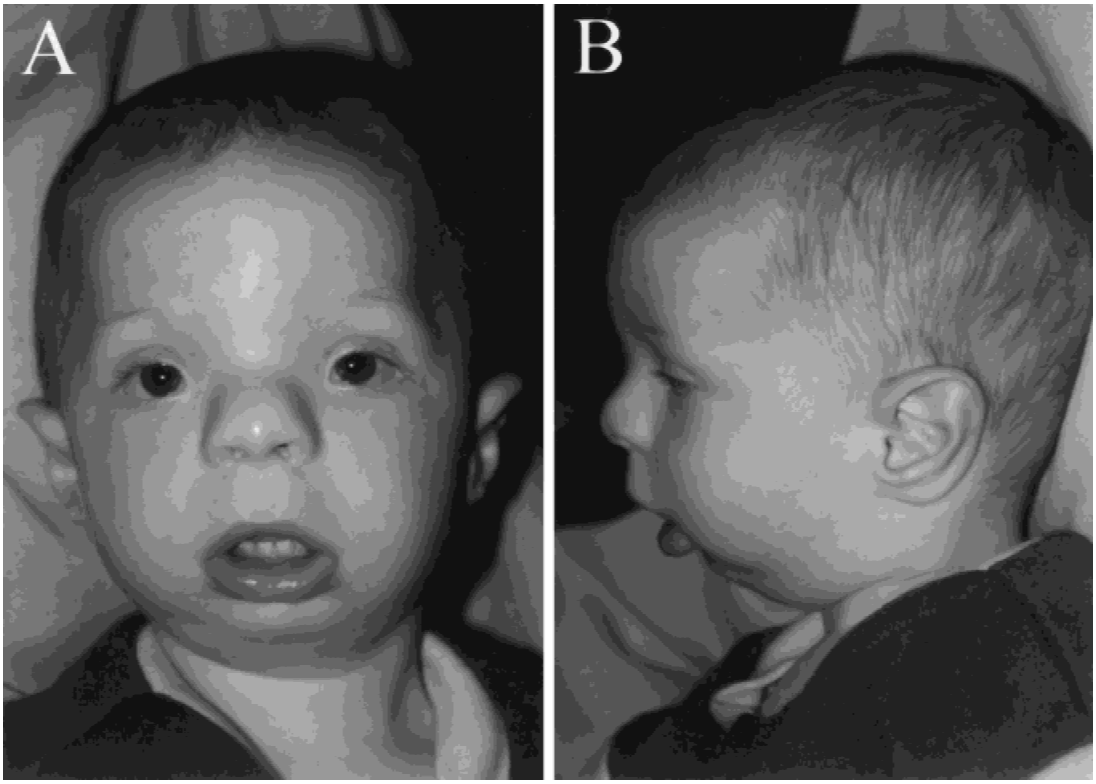

Fig. 1. Shown are AP **(A)** and lateral **(B)** views of face at age 1 year, including hypertelorism with mild frontonasal malformation, micrognathia, mild ptosis, and posteriorly angulated ears.

monary status was normal. Abdominal findings were normal, as were external genitalia. His back was straight with no defects. Digits, nails, hair, and skin texture were normal. Neurological status was appropriate for age. Cranial ultrasonography shortly after birth showed no evidence of frontal encephalocele or focal abnormalities, with an intact corpus callosum. At 4 years of age his phenotype was unchanged (Fig. 2).

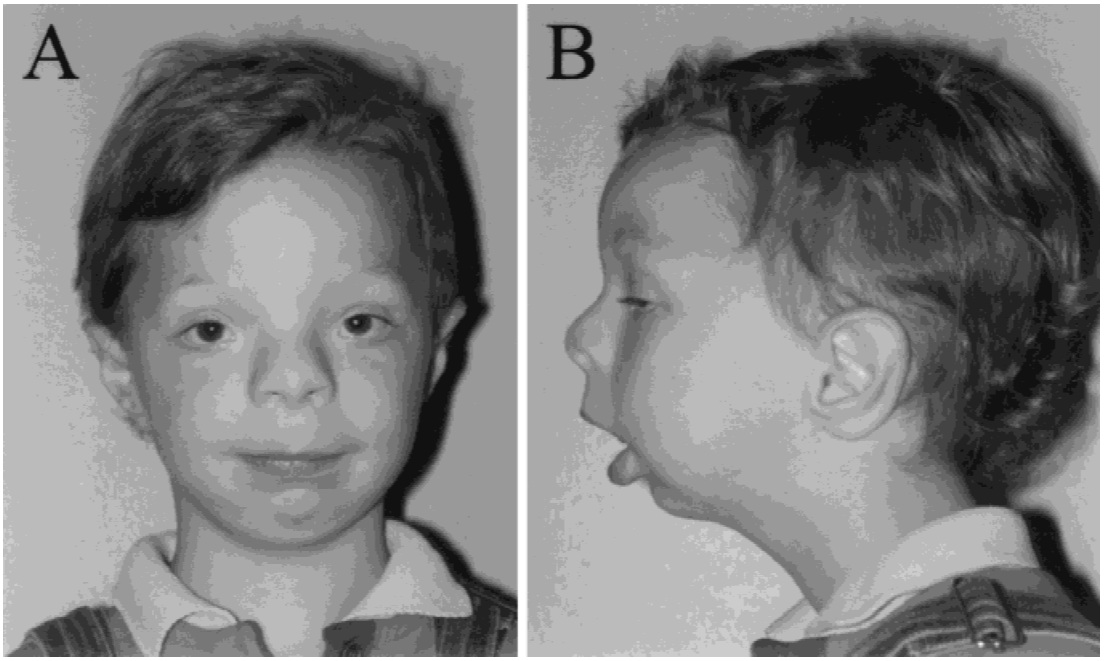

Fig. 2. Shown are AP **(A)** and lateral **(B)** views for facial phenotype at age 4 years.

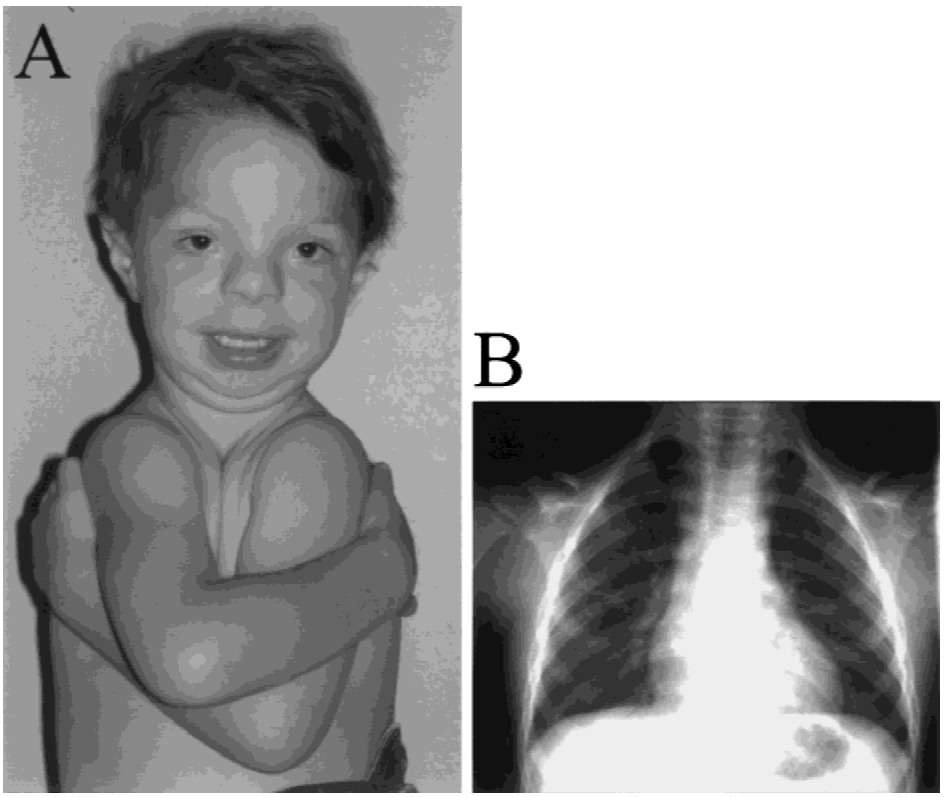

Fig. 3. The clavicular hypoplasia as documented clinically by hypermobile shoulders **(A)** and on chest radiograph **(B)** at age 4 years is shown. Note the severely hypoplastic clavicles visible above the scapulae bilaterally.

The previously noted midline alveolar diastema had caused significant spacing between the central incisors. Severe mandibular retrusion and a class II malocclusion became apparent, resulting in a large, open anterior bite. At 4 years, he was noted to have hypermobile shoulders suggestive of clavicular hypoplasia (Fig. 3A). Hypoplastic clavicles were seen on a plain film, with each clavicle having a segment of about 2.0 cm lying superior to the coracoid process and lacking a medial segment (Fig. 3B). He was assessed as having above-average intellect, with an extensive vocabulary and an outgoing, conversant nature.

Three-dimensional CT scan of the head demonstrated orbital hypertelorism, diastema of the maxillary midline with lateral displacement of the central incisors, underdeveloped nasal bones, micrognathia with bilateral condylar head hypoplasia, upward deviation of small central incisors with anterior open bite,

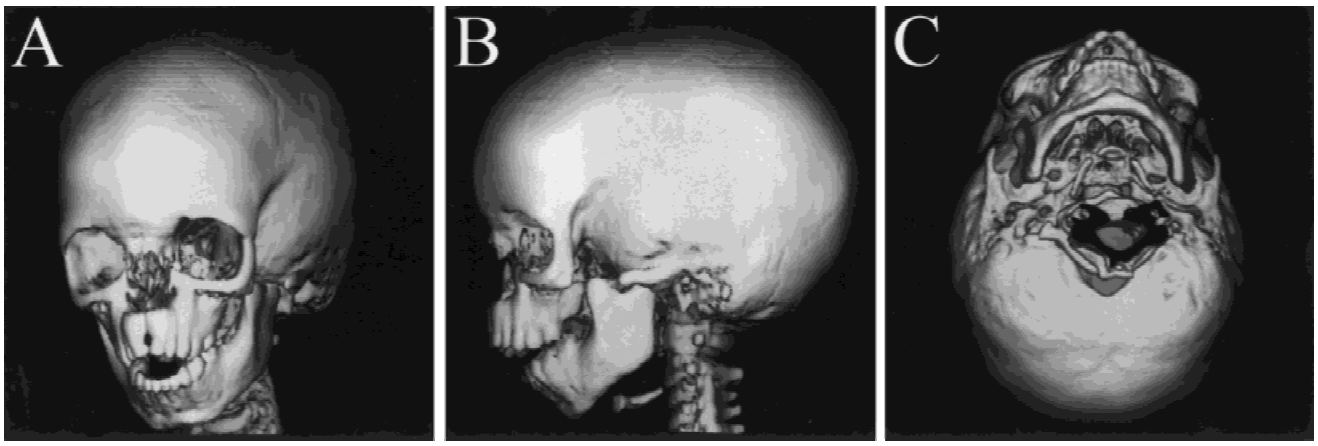

Fig. 4. Shown are the three-dimensional CT scans at age 4 years: Left three-fourths view shows absent nasal bones, orbital hypertelorism, absent zygomatic arches, and midline maxillary cleft **(A)**. Lateral view demonstrates micrognathia with condylar hypoplasia, anterior open bite, and absence of zygomatic arches **(B)**. Inferior cranial base view demonstrates the absence of the zygomatic portions of the zygomatic arches with preservation of the temporal component as well as a large incisive foramen **(C)**.

TABLE I. Comparison of case with known CCHA and MFD syndromes*

Findings	C.G.	CCD	8q22 r.	PFCH	MAD	YV	TC	Nager	Miller
Wide/unossified sutures, open fontanelles		X[a]	X	X	X	X			
Wormian bones		X[a]	X		X				
Metopic ridge	X		X						
Bilateral enlarged parietal foramina				X[b]					
Sparse hair on scalp/face					X	X[d]			
Microcephaly						X			
Hypoplastic zygomatic arches	X	X					X		
Craniofacial disproportion	X	X	X			X			
Nasal bone hypoplasia	X	X	X						
Hypertelorism	X	X	X	X		X			
Frontonasal dysplasia	X	X	X						
Antimongoloid slant of palpebral fissures							X[e]		X[g]
Coloboma of upper or lower lids							X[e]		X[g]
Lower lid ectropion									X
Deficient eyelashes							X		X
Microcornea	X								
Stellate irises	X								
Malar hypoplasia							X[e]	X[f]	X[g]
Broad, bulbous nose	X	X							
Thin, beaked nose					X				
Flattened frontonasal angle, aquiline nose							X		
Choanal atresia							X		
Thick frenulum	X								
Incisive foramen cyst	X	X							
Macrostomia							X		
High-arched palate	X	X	X		X	X	X		
Cleft palate/lip		X	X				X	X[f]	X[g]
Macrostomia							X		
Supernumary teeth, other dental anomalies		X[a]			X	X	X		
Maxillary hypoplasia	X	X	X	X		X	X		
Midline cleft in maxilla	X								
Micrognathia	X		X		X	X	X[e]		X[g]
Hypoplastic or malformed ears							X[e]		X[g]
Middle/inner ear defects, variable deafness							X[e]	X[f]	
Clavicular hypoplasia/aplasia	X	X	X	X	X	X			
Polythelia									X
Absence/malformation of digits		X	X		X[c]	X[d]		X[f]	X[g]
Absence/malformations of (esp. big) toes			X			X[d]		X	X[g]
Limb deformities, preaxial								X[f]	
Limb deformities, postaxial									X[g]
Acroosteolysis					X				
Joint stiffness					X[c]				
Atrophic skin					X[c]				
Short stature/growth retardation		X[a]	X	X	X	X[d]			
Visceral involvement						X	X		X
Intellectual/development delays						X			X
Normal karyotype	X	X	X	X	X	X			
Associated genetic findings		6p21 md.	8q22 r.						

*Manifestations in our case, including microcornea, stellate irises, a thick frenulum, and a midline maxillary cleft, are unique among those seen in five closest-fit CCHA syndromes. Our patient lacks important clinical and radiological findings, including major diagnostic criteria, for each.

CCD, cleidocranial dysplasia; PFCH, parietal foramina clavicular hypoplasia; MAD, mandibuloacral dysplasia; YV, Yunis-Varon syndrome; TC, mandibulofacial dysostosis, Treacher Collins type; Miller, Miller syndrome/acrofacial dysostosis, postaxial type. References cited in composing this table include Ades et al. [1993], Brueton et al. [1992], Chitayat et al. [1992], Eteson [1984], Eventov et al. [1979], Frame and Evans [1989], Garrett et al. [1990], Golabi [1984], Goodman et al. [1975], Hall [1982], Hasler and Vandermer [1974], Hennekam and Vermeulen-Meiners [1989], Jackson [1951], Jarris and Keats [1974], Jenson and Kreiborg [1993b], Keats [1967], Lapeer and Fransman [1992], Morgenstein and Becker [1971], Mundlos et al. [1997], Myers [1982], Narahara et al. [1995], Nienhaus et al. [1993], Partington [1982], Pfeiffer et al. [1988], Seftel et al. [1996], Sharma et al. [1995], Stevenson [1993], Toriello [1982a,b], Toriello [1991], van Heest [1996], Walker and Bocian [1987], Wiedeman et al. [1997], Yunis and Varon [1980], and Zackai et al. [1997].

[a]Major diagnostic criterion for CCD [Mundlos et al., 1995; Myers, 1982].

[b]Major diagnostic criterion for PFCH [Toriello, 1982a].

[c]Major diagnostic criterion for MAD [Toriello, 1982b].

[d]Major diagnostic criterion for YV [Partington, 1982].

[e]Major diagnostic criterion for TC [Wiedemann et al., 1997].

[f]Major diagnostic criterion for Nager syndrome [Wiedemann et al., 1997].

[g]Major diagnostic criterion for Miller syndrome [Wiedemann et al., 1997].

bilateral absence of the zygomatic component of the zygomatic arches, and an enlarged incisive foramen (Fig. 4A–C). CT scan of the brain was normal. There were neither Wormian bones nor supernumerary teeth evident on three-dimensional CT scan, flat radiograph, or dental radiographs. The heart, mediastinum, and lungs were normal on chest radiograph. Renal ultrasound findings were normal.

Laboratory test results were normal. Chromosomes demonstrated a 46,XY constitution at a 550-band resolution, and no mutation was found on genomic sequence analysis of the CBFα1 gene.

DISCUSSION

Our patient has a unique phenotype that includes CCHA, mild frontonasal malformation, micrognathia, and hypoplastic zygomatic arches. A literature search failed to identify cases with a similar presentation, especially in light of our patient's normal intelligence, normal stature, and lack of limb or visceral involvement. However, some similarities do exist within the 7 closest-fit CCHA and MFD syndromes, as seen in Table I. Congenital anomalies of the clavicle are uncommon; their presence should prompt the search for other abnormalities that will allow recognition of a specific disorder [Moseley, 1968]. It is noted that there are no reported associations between MFD and hypoplastic or absent clavicles.

Cleidocranial dysplasia, cases of 8q22 cytogenetic rearrangements, and our case all demonstrate varying degrees of frontonasal malformation. In describing the craniofacial abnormalities of several cleidocranial dysplasia patients, Jensen and Kreiborg [1993a] present photographs of several affected dry skulls. An external cranial base view of an affected skull allows the reader to appreciate the presence of both poor anterior midface growth and an enlarged incisive foramen, similar to our patient. The enlarged appearance of this foramen in these skulls is likely secondary to a lack of ventral maxillary growth and subsequent ventral angling of the foramen. Our patient also clearly has micrognathia and zygomatic arch malformations, findings seen in patients with Treacher Collins, Nager, and Miller syndromes, 8q22 cytogenetic rearrangements, mandibuloacral dysplasia [Toriello, 1982b], and Yunis-Varon syndrome but not those with cleidocranial dysplasia [Partington, 1982]. Micrognathia has been reported in over 130 syndromes and 47 chromosomal anomalies [Stevenson et al., 1993], including non-CCHA patients with partial duplications of chromosome 8 [Walker and Bocian, 1987].

In an investigation of young and adult patients with cleidocranial dysplasia, the zygomatic arch was slender and less prominent in all patients studied, and incomplete in up to 50% of patients [Jensen and Kreiborg, 1993a]. Dry skull photographs of cleidocranial dysplasia patients show incomplete formation of the zygomatic portion of the arches as well as underdeveloped posterior arch roots and reduced upper facial height, particularly in adult patients. A study of infant skull development in cleidocranial dysplasia by the same authors presents a patient's craniofacial three-dimensional CT scans [Jensen and Kreiborg, 1993b]. Incomplete anterior zygomatic arch development is evident in both lateral and inferior cranial base views. Treacher Collins, Nager, and Miller syndromes also demonstrate hypoplastic zygomata, a component of very characteristic "birdlike" facies. This facial dysmorphism also includes malar, maxillary, and mandibular hypoplasia, causing the cheeks to appear sunken with a narrow, receding chin [Wiedemann et al., 1997].

In searching for a possible common pathogenesis among the 6 different syndromes (Table I), the cleidocranial dysplasia–CBFα1 relationship and 8q22 rearrangement phenotypes serve as reference points. The phenotype associated with CBFα1 mutations has been well documented. A review of the phenotypic correlations in more than 80 patients with various partial duplications of 8q [Walker and Bocian, 1987] showed abnormal skull shape with prominent forehead, hypertelorism or telecanthus, long philtrum, broad nasal root, cardiac lesions, various vertebral and rib abnormalities, broad, short neck, renal malformations, camptodactaly, brachydactaly, micrognathia, and high-arched or cleft palate. This review included 2 siblings with duplication of the segment 8q12–8q21.2 and mild micrognathia, high or posterior cleft palate, telecanthus, mild microcephaly, severe developmental delays, and cardiac malformations; both died at age 4 months. Interestingly, neither had clavicular abnormalities [Brueton et al., 1992]. It is possible that variant mutations of the same gene or family of genes could lead to distinct phenotypes with multiple common features as seen earlier.

In summary, our patient represents a previously unreported phenotype with CCHA and MFD, with distinct findings in comparison to several established CCHA and MFD syndromes. We have suggested the acronym CHZAM (clavicular hypoplasia, zygomatic arch, and mandibular hypoplasia) to represent this unique phenotype that appears to be on a continuum of alternative mutations leading to a wide variety of CCHA and mandibulofacial dysostosis presentations.

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